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View Article Online
DOI: 10.1039/C8CC00207J

Journal Name

COMMUNICATION

Imido-P(V) Trianion Supported Enantiopure Neutral Tetrahedral Pd(II) Cages

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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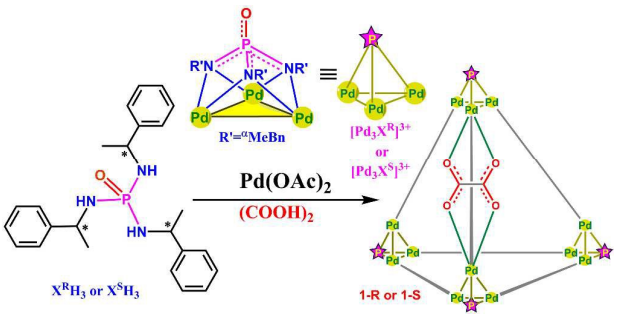
Charge-neutral chiral hosts are attractive due to their ability to recognize a wide range of guest functionalities and support enantioselective processes. However, reports for such charge-neutral cages are very scarce in the literature. Here, we report an enantiomeric pair of tetrahedral Pd(II) cages built from chiral tris(imido)phosphate trianions and oxalate linkers, which exhibit enantioselective separation capabilities for epichlorohydrin, β-butyrolactone, 3-methyl- and 3-ethyl cyclopentanone.

Chiral recognition is a fundamental phenomenon in nature which plays a vital role in many chemical and biological functions.[1] Current efforts in this area have been devoted towards the synthesis of artificial chiral architectures and utilize them in a manner akin to natural systems.[2] Over the years, several synthetic receptors such as capsules, cages, porous materials and supramolecular polymers are pursued for this purpose.[3] In this regard, discrete and well defined coordination-driven self-assemblies or metal-organic cages (MOCs) exhibiting chirotopic spaces offer great potential for enantioselective recognition, sensing, separation as well as asymmetric catalysis.[4-5] The uniqueness of these cage assemblies stems from their ready synthesis and the presence of their cavities that can exhibit exceptional recognition and discrimination of guest molecules from the bulk solution. Chirality in MOCs is typically achieved (a) by the use of organic stereo-centers at the ligand backbone, (b) by the presence of stereogenic transition metal ions and (c) by employing achiral ligands that favour axial or helical chirality.[6]

Most of the known chiral MOCs are charge-separated (anionic or cationic) moieties derived from the self-assembly of geometrically prefixed metal-nodes and directional bridging ligands and take-up the topologies of a regular polyhedron.[7] Anionic M_4L_6 cages have been used for chiral recognition and catalytic reactions such as aza-cope rearrangement and terpene-cyclization reactions,[8] while cationic M_6L_4 cages performed asymmetric thermal and photochemical reactions.[9] Examples of certain axially chiral Fe_4L_6 and Fe_4L_4 assemblies have also been employed for recognition of chiral organic molecules.

Recently, a few examples of neutral tetrahedral cages with axial chirality supported by bis-diketonate linker ligands were shown to resolve small racemic alcohols through co-crystallization.[10] Soluble in organic solvents charge-neutral cages with chiral pockets are particularly desirable as they can recognize a wide range of functional groups and support the enantioselective processes in a continuous and recyclable manner. However, owing to the challenges associated with the large-scale synthesis of the chiral cages in optically pure form, there are only a limited number of MOCs (cationic, anionic or neutral) that can support enantioselectivity based studies.[4-5, 8-10]



Scheme 1: Synthesis of enantiopure cages **1**-R and **1**-S from the chiral ligands X^RH_3 and X^SH_3, respectively.

Herein, we describe the synthesis of enantiomeric tetrahedral cages, R- and S-$[(Pd_3X^*)_4L_6]$, supported by chiral trianionic capping ligands $[X^*]^{3-}$ = $[PO(N(^*CH(CH_3)Ph)_3]^{3-}$. These cages were found to separate enantiomers of various small molecules with functional groups such as epoxide, ketone and lactone.

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†Electronic Supplementary Information (ESI) available: Experimental procedures and characterisation data. CCDC 1574961, 1575098, 1575099, 1575442 contains the crystallographic data and other electronic format See DOI: 10.1039/x0xx00000x

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The chiral phosphoramide precursors, (R,R,R)-(+)-*N,N′,N″*- and (S,S,S)-(–)-*N,N′,N″*-PO(NH(*CH(CH_3)Ph)$_3$, denoted as X^RH_3 and X^SH_3, were prepared from the corresponding R- and S-α-methylbenzylamine ($^{\alpha}$MeBnNH$_2$) and $POCl_3$ (Scheme S1). The optical activity of the ligands has been confirmed by circular dichroism (CD) in DCM and X-ray structure analysis (Figure 1 and Figures S1-S5, ESI). Treatment of $Pd(OAc)_2$ with the respective phosphoramide (X^RH_3 or X^SH_3) in the presence of oxalic acid (LH_2) in DMSO gave the neutral cages R-[$(Pd_3X^R)_4L_6$] (**1**-R) and S-[$(Pd_3X^S)_4L_6$] (**1**-S) in good yields (Scheme 1). The MALDI-TOF mass spectrum of both **1**-R and **1**-S in DCM gave an isotopic distribution of peaks centered at m/z 3462 corresponding to their $[M+K]^+$ ions (Figure S6, ESI). The ^{31}P NMR spectra of cages **1**-R and **1**-S showed a singlet at 71.3 ppm, while ^{1}H NMR spectra gave well resolved signals for the ligand environments at both the aliphatic and the aromatic regions which are marginally shifted downfield with respect to the free ligands. Their ^{13}C NMR showed a single peak at 173.7 ppm suggestive of a symmetric environment of the oxalate ligands (Figure S7-S9, ESI). These compounds exhibit good thermally stability; they decompose above 250 °C (Figure S10, ESI).

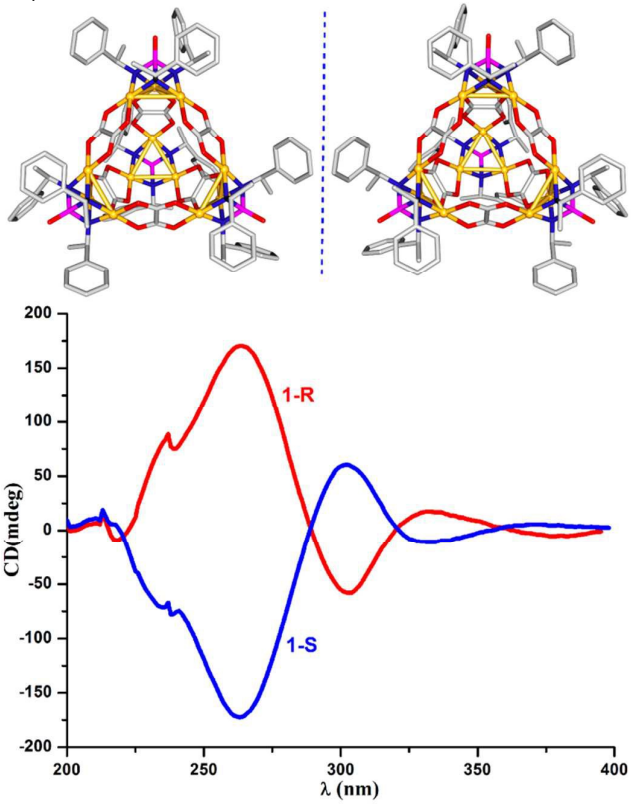

Figure 1: (SCXRD derived Structures of **1**-R (top left) and **1**-S (top right) and their corresponding Circular dichroism spectra (bottom). Color code: Pd, Orange; C, gray; N, blue; O, red; P, magenta.

The CD spectra of **1**-R and **1**-S in DCM show that the cages are enantio-enriched as they exhibit mirror image signals. For each enantiomeric cage, bisignate bands at 264 (π-π*), 302 (MLCT), 332 (MLCT) nm were observed (Figure 1, bottom). The observed absolute configuration (α_D) values of +666° and -684° for **1**-R and **1**-S, respectively, were significantly higher than those of the corresponding phosphoramides (+23°, X^RH_3 and -25°, X^SH_3).

Crystals of **1**-R and **1**-S suitable for single crystal X-ray diffraction (SCXRD) analysis were obtained from slow evaporation of their DCM solutions. The structural determination of these crystals confirmed the absolute configurations of **1**-R and **1**-S. They crystallized in the cubic chiral space group *F*23 (Figure 1, top image) mirroring the symmetry of the chiral tetrahedral cages (*T*). The Pd_3X^*-units constitute the corners of the tetrahedron, while the oxalate ligands are linking them across its edges. The wide-angle chelation of the oxalate ligands offer perfect coordination for the 90° cisoidal sites at the Pd_3 units. The Pd_3X units exhibit trigonal symmetry; their α-Me groups attached to the stereogenic carbon centers are oriented either clockwise (in **1**-R) or anticlockwise (in **1**-S). The crystal structures showed the presence of large solvent accessible voids both inside and outside of the cages, which amount to 51 %, which is 13051 Å^3 of the total unit-cell volume (Figures S11-S14, ESI). MSROLL calculations gave 86 Å^3 as the intrinsic volume of the cavity which is comparable to the isostructural achiral [$(Pd_3X)_4L_6$] cage (Figure S15 and Table S3, ESI).[11]

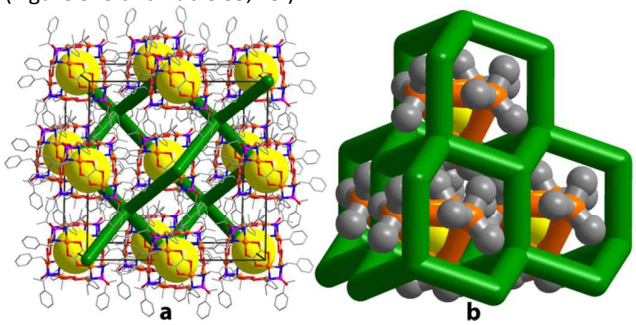

Figure 2: (a) The packing diagram of **1**-S showing the 3D-network of channels as green links. The yellow spheres represent the intrinsic cavity. (b) View of the diamondoid network formed by the external channels; the frameworks of the cages are represented as orange tetrahedral frames and chiral R-groups as grey spheres.

The void structure of the crystals of **1**-R and **1**-S is remarkable in that it consists of an open 3D-network of diamondoid channels that is running externally of the cages, while the internal voids of the cages are linked to this external network. This loose packing is only supported by hydrophobic interactions between peripheral methylbenzyl groups. It is reminiscent to that of nanoporous crystals of awkwardly shaped molecules.[12, 13] However, these crystals are not stable and will disintegrate to a denser, amorphous form upon desolvation. Nevertheless, the denser form still shows some porosity: CO_2 adsorption data at 195 K reveal a moderate uptake of 2.7 mmol/g. The BET surface area amounts to 450 m^2/g and DFT derived pore size analysis suggests a pore diameter of 3.5 Å (Figure S31-33, ESI).

The presence of voids, both intrinsic and extrinsic, prompted us to investigate the encapsulation of chiral molecules. The

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Dichloromethane solutions of **1**-R and **1**-S, respectively, were treated with racemates of (±) epichlorohydrin (epi), β-butyrolactone (bbl), 3-methyl cyclopentanone (3-Me-cp) and 3-ethyl cyclopentanone (3-Et-cp) yielding the corresponding host-guest assemblies as opaque crystalline solids. The MALDI-TOF mass spectral analysis recorded in DCM solutions of all these solids gave the isotopic distribution of peaks at 3538, 3538, 3533, and 3533 corresponding to ±epi⊂**1**-R, ±epi⊂**1**-S, ±bbl⊂**1**-R and ±bbl⊂**1**-S, respectively. Also, broad peaks centred at 3522, 3522, 3535 and 3535 have been observed for ±3-Me-cp⊂**1**-R, ±3-Me-cp⊂**1**-S, ±3-Et-cp⊂**1**-R and ±3-Et-cp⊂**1**-S assemblies (Figures S16-S21, ESI). The ^{1}H-NMR spectra of ±epi⊂**1**-R and ±bbl⊂**1**-R showed prominent chemical shifts for the guest protons (Figures S22 and S23, ESI) indicating the formation of host-guest assemblies upon crystallization. The ^{1}H-2D-diffusion ordered spectroscopy (DOSY) studies suggest that the guest molecules are not firmly bound to the hosts at their intrinsic cavities but are loosely associated with the exterior of the cage (Figures S24-S27, ESI). Unfortunately, the crystals of the host-guest complexes were not of sufficient quality for X-ray structure analysis.

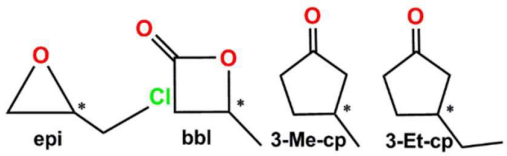

Figure 3: Guest molecules used in the chiral recognition studies.

Since the structural analysis of the denser chiral material and the host-guest complexes remained unsuccessful, we attempted to crystallise the corresponding racemates (**1**-R + **1**-S) to probe if they exist in a similarly dense form and, thus, may provide some insights into the host-guest interactions. We were able to obtain crystals from the system ±bbl⊂±**1** that were suitable for X-ray analysis (Figure 4). They crystallised in space group *Cc* exhibiting the composition $[(Pd_3X)_4L_6]\cdot(bbl)_{9.5}\cdot(H_2O)$. The structural analysis revealed that it contains a 1:1 mixture of **1**-R and **1**-S cages which form packings that are about 1.37 times denser (via Z/V) than in the enantiopure cubic crystals. Although one has to accept the limitations of a direct comparison between the packing of the enantiopure and the racemic materials, the racemic structure shows some interesting properties that may shed some light on the structure of the chiral host-guest complexes. The crystal structure of the racemic host-guest compound still contains significant external void space of 32% which amounts to 5002 Å^3 of the unit cell volume and the computed intrinsic void was again found to be 88 Å^3 per cage molecule. The bbl guests were found at both the intrinsic and extrinsic cavities of the cages exhibiting both ordered and disordered arrangements. The majority of the ordered guest molecules were located in the external cavities at pockets formed by the optically active methylbenzyl groups and the oxalate ligands indicating potential interactions for chiral recognition.

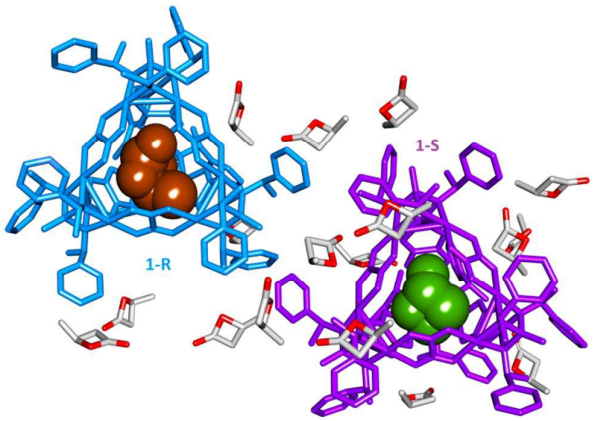

Figure 4: View of the location of bbl guests in the structure of ±bbl⊂±**1**. Only the ordered bbl molecules located close to chiral centres are shown here. The bbl molecules at the intrinsic voids are depicted as space-fill models.

The enantioselective separation capabilities of **1**-R and **1**-S for the above mentioned racemic substrates were evaluated by gas chromatography (GC) analysis. For the GC experiments, the guest molecules were first mixed with the DCM solutions of apohosts and left for evaporation at room temperature. The obtained inclusion solids were washed with diethyl ether and the guest molecules were subsequently desorbed by treatment with methanol. The chiral GC analyses of ±epi, ±bbl, ±3-Me-cp and ±3-Et-cp desorbed from **1**-R by washing with methanol yielded the respective enantiomeric excess (*ee*) values of 6, 34, 14 and 12 %, with the R enantiomers being in excess (Table S4, Figures S34-S45 ESI). Similar experiments with the **1**-S cage yielded an *ee* of 10, 14, 16, and 14 % for the respective excess S-enantiomers (Table S4). A change in size did not seem to affect the enantioselectivities observed for the two ketone guests probed in this study irrespective of the chirality of the host cage. The lower *ee* values obtained for other assemblies might be attributed to the poor binding of the guest molecules to the host cages as some amounts of the bound guests could also be lost during the initial diethyl ether washing.

Control experiments showed that the ligands, L^{1R} and L^{1S}, alone could not resolve the enantiomers of the examined substrates under identical conditions, indicating that the more open structure of the chiral cage assembly plays a role in the enantioselective recognition and separation. Notably, the cage assemblies of **1**-R and **1**-S can be regenerated after each separation experiment either by heating to 100°C or drying under vacuum overnight followed by recrystallisation from DCM at room temperature. The recrystallized cages can then be directly used for subsequent separation runs which showed similar *ee* values. This indicates that the cage assemblies are very robust as the apohosts can be regenerated after guest desorption and reused without any apparent performance loss. The structural and optical robustness of these cages were further confirmed by CD spectra, optical rotation and single-crystal X-ray diffraction analysis performed on recrystallised samples of **1**-R and **1**-S (Figure S46, Tables S5 and S6, ESI). The separation efficiencies of these chiral cages are comparable with some of the previously reported best performing metal-

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ligand discrete assemblies.[4] Previously reported methods described the separation of epoxides via hydrolytic kinetic resolution.[14] In contrast, our cage assemblies have been shown to resolve ±epi in a more direct fashion.

In conclusion, we have synthesized enantiopure tetrahedral cages **1**-R and **1**-S. These were found to promote enantioselective separation of small racemic molecules having varied functionalities such as epoxide, lactone and ketone via crystallization inclusion. Single crystal X-ray analysis of ±bbl@±**1** showed that guest recognition predominantly takes place at the extrinsic cavities of the cage. Currently, we are focussing on generating new examples of chiral cages with varied polyhedral shapes and cavity sizes for chiral separation of larger substrates in solution and in the solid state as well as performing asymmetric transformations in their chiral pockets.

This work was supported by SERB, India through Grant No. EMR/2016/000614 (R.B.). P.R. thanks the UGC, India for the fellowship. We thank Dr. S. Chikkali for providing access to GC measurements and Dr. R. Vaidhyanathan for adsorption measurements.

Conflicts of interest

There are no conflicts to declare.

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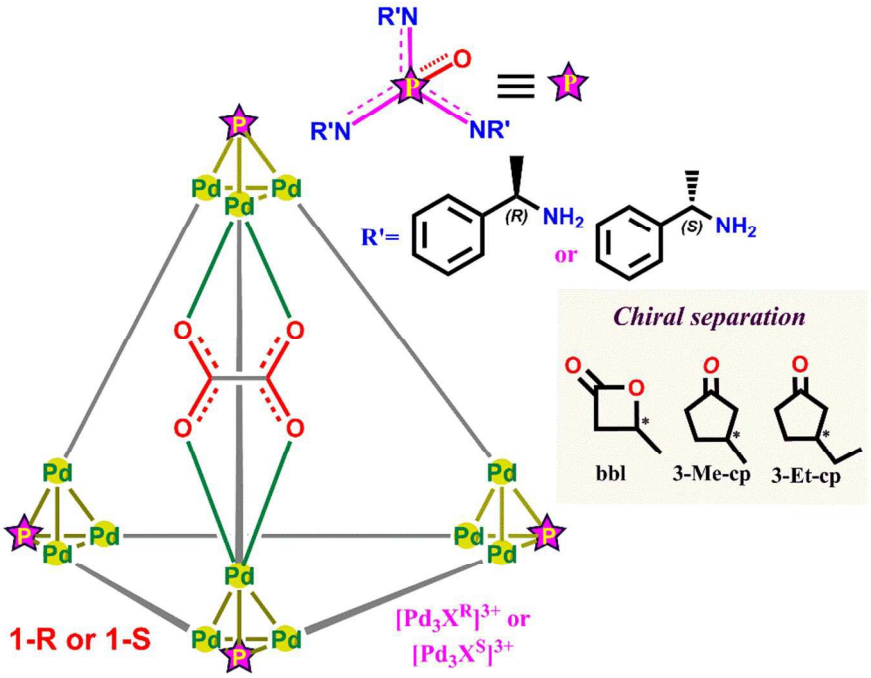
Graphical Abstract



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